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PHARMACOMETRICS

Interaction Between Structural, Statistical, and Covariate Models in Population Pharmacokinetic Analysis

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The influence of the choice of pharmacokinetic model on subsequent determination of covariate relationships in population pharmacokinetic analysis was studied using both simulated and real data sets. Simulations and data analysis were both performed with the program NONMEM. Data were simulated using a two-compartment model, but at late sample times, so that preferential selection of the two-compartment model should have been impossible. A simple categorical covariate acting on clearance was included. Initially, on the basis of a difference in the objective function values, the two-compartment model was selected over the one-compartment model. Only when the complexity of the one-compartment model was increased in terms of the covariate and statistical models was the difference in objective function values of the two structural models negligible. For two real data sets, with which the two-compartment model was not selected preferentially, more complex covariate relationships were supported with the one-compartment model than with the two-compartment model. Thus, the choice of structural model can be affected as much by the covariate model as can the choice of covariate model be affected by the structural model; the two choices are interestingly intertwined. A suggestion on how to proceed when building population pharmacokinetic models is given.

KEY WORDS: population pharmacokinetics; structural model; covariate model; NONMEM; model selection.

INTRODUCTION

The population approach for pharmacokinetic data analysis, as implemented within the program NONMEM (1), was originally proposed for the analysis of sparse data (2). As such, it was not originally intended to be

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used as a tool for selection of the structural (pharmacokinetic) model. The choice of structural model was to be based upon the best a priori information about the drug to be studied, or a simple model was to be used when the nature of the data was such that a more complex model could not be supported. Population pharmacokinetic analysis, having gained widespread acceptance, is used for analysis of both sparse and more intensively sampled data sets, but the initial selection of the structural model is still somewhat arbitrary. A review of 30 pharmacokinetic data analyses (3–32) in which NONMEM was used revealed that only one-third reported statistical justification for the choice of structural model. The investigators that did report a reason for their choice of structural model did not consider that the choice made may have had any influence on subsequent statistical or covariate model building. Whether or not an attempt is made to justify the selection of the structural model, there usually exists an implied and untested assumption that the relationships between "model-independent" parameters (such as clearance) and covariates are unaffected by the structural model.

Simple pharmacokinetic models may be used for a variety of reasons, the most obvious being that a more complicated model cannot be justified statistically. For example, the limit of assay sensitivity may preclude characterization of longer terminal phases of drug elimination, or data obtained at steady state may be insufficient to enable characterization of a distribution phase. Within the field of therapeutic drug monitoring, simple pharmacokinetic models are routinely used for prediction purposes. For example, samples taken for the optimization of digoxin therapy are intentionally obtained after the distribution phase. Again, in these different situations, the covariate–pharmacokinetic relationships are assumed to be unaffected by the pharmacokinetic model itself.

This paper seeks to examine the influence of the choice of structural model on the subsequent building of the covariate model. Initially, we studied simulated data sets (see "Simulations"). Analysis of the simulated data revealed that the issue was more complex than originally thought and led us to reconsider criteria for choosing the structural model itself. Analysis of two real data sets (see "Real Data") exemplify the issues encountered with the simulations. Finally, the implications of the results are discussed.

SIMULATIONS

Data

Data were simulated using the program NONMEM (Version IV), using a two-compartment model with intravenous input (ADVAN3, TRANS3) (1). The values of the pharmacokinetic parameters were loosely based upon

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those of digoxin. For each of 100 subjects, clearance (CL) was sampled from a normal distribution characterized by a population mean of 11.3 L/hr, and constant coefficient of variation (ω_{CL}) of 25%; volume of the central compartment (Vc) was sampled from a normal distribution characterized by a population mean of 37.6 L, and ω_{Vc} of 30%. No covariance between CL and Vc was included. Intercompartmental clearance (Q) and volume of distribution at steady state (Vss) were fixed to be 31.4 L/hr and 470 L, respectively, for all subjects. The values of the pharmacokinetic parameters were such that the typical values for $t_{1/2(\alpha)}$ and $t_{1/2(\beta)}$ were 35 min and 36 hr, respectively. A proportional random normal error (10%) was added to each concentration.

A second series of data was also simulated with a simple dichotomous covariate (e.g., presence of an interacting drug) affecting CL in a subset of individuals within each data set. Two subpopulations were created, one ($n=75$) with a mean CL of 11.3 L/hr (e.g., monotherapy), and another ($n=25$) with a mean CL of 14.2 L/hr (e.g., in the presence of an interacting drug).

The goal was to simulate data after a borderline time point, with which a two-compartment model could no longer be preferentially selected. Thus, data within four different time ranges (3–120 hr, 6–120 hr, 12–120 hr and 48–120 hr) were tried. Each subject had three samples selected randomly from a series of fixed time points within the time ranges. Fifty data sets, each consisting of 100 subjects, were generated for each time range and for each of the two situations, without and with the drug interaction covariate influencing CL (in a subset of individuals).

Analysis

Data analysis was carried out in two stages. First, to find the borderline time point (after which a two-compartment model could no longer be justified statistically with the simulated data), one- and two-compartment models were fit to all the data sets. The analysis included a covariate effect only when the effect was simulated in the data. Second, after the borderline time point was identified, different covariate models with both the one- and two-compartment models were fit to the data simulated after this point.

Model selection was based on the objective function value of the reduced model minus that of the full model, which approximates the difference in minus twice the maximum log likelihood of the two models. The difference is approximately chi-square distributed.

Enigma

The frequency of selecting the two-compartment model, with and without the covariate in CL, was much larger than would be expected for

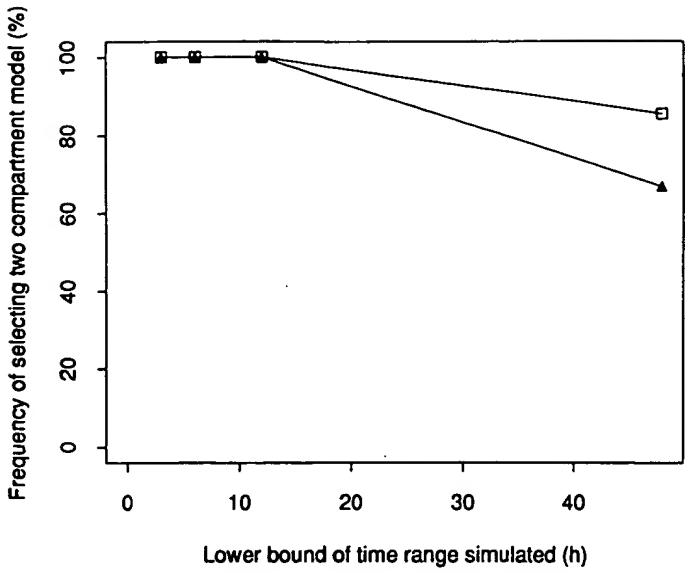

Fig. 1. The percentage of data sets simulated between the time indicated and 120 hr, in which a two-compartment model was selected (based on $p \leq 0.05$) over a one-compartment model. The squares are the percentages associated with the data that included the drug interaction covariate on *CL* in both the simulation and analysis; the triangles are the percentages when no covariate was present.

each of the four time ranges studied (Fig. 1). For example, because the $t_{1/2(\alpha)}$ was only 35 min, data simulated between 48–120 hr were over 80 half-lives after the end of the distribution phase, making the selection of the two-compartment model appear nonsensical. No matter what the borderline time point was, the two-compartment model was virtually always selected, making the objective of finding the borderline between the one- and two-compartment models impossible to attain.

Resolution of the Enigma

For each set of two-compartment parameter values used in the simulations, we determined the values of *CL* and volume (*V*) corresponding to the exponential associated with the terminal slope (analogous to treating data originating from the terminal phase of a two-compartment model as if it originated from a one-compartment model). Two findings resulted from these calculations. First, the drug interaction covariate influenced *V* as well as *CL*. Second, a high correlation between *CL* and *V* was found. (Recall, the simulation of two-compartment parameters assumed no correlations.)

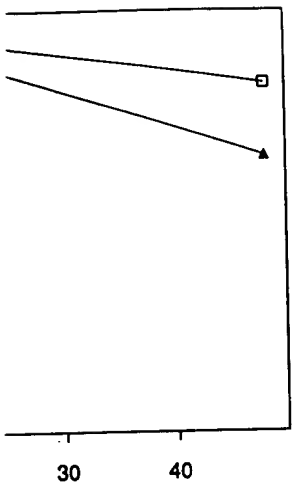

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Table I. Mean Difference (and SD) in the Objective Function Values of the One- and Two-Compartment Models, for the Fifty Replicate Data Sets[a]

True covariate model (Simulation)	Covariate model (Analysis)	Statistical model (Analysis)	Time range of simulated data (hr)			
			3–120	6–120	12–120	48–120
No covariate on CL	No covariate on CL	No covariance between CL and Vc (V)	272 (41)	99.5 (18)	60.1 (19)	7.1 (25)
No covariate on CL	No covariate on CL	Covariance between CL and Vc (V)	235 (39)	10.9 (7.7)	0.6 (2)	0 (0)
Covariate on CL[b]	Covariate on CL	No covariance between CL and Vc (V)	300 (41)	112 (24)	71.7 (23)	19.3 (28)
Covariate on CL	Covariate on CL	Covariance between CL and Vc (V)	263 (40)	24.4 (16)	16.4 (12)	5.0 (5.8)
Covariate on CL	Covariate on CL and V[c]	Covariance between CL and Vc (V)	250 (40)	8.6 (11)	1.3 (5.7)	0.6 (3)

[a]Regarding the difference in degrees of freedom between the one- and two-compartment models as two, a difference in the objective function values of 5.99 corresponds to a p of 0.05.
[b]For data sets simulated with a simple categorical covariate in CL, 25% of the subjects had a 25% increase in CL.
[c]For the one-compartment model, the covariate acts on CL and V; for the two-compartment model, the covariate acts on CL only.

The data simulated for the purpose of finding the borderline time point were then reanalyzed. First, a covariance between CL and V was included in the one-compartment model. In the case where no covariate had been included in the simulated data, inclusion of the covariance between CL and V was sufficient to enable the one-compartment model to be selected (Table I). With the simulated data that contained the drug interaction covariate, the two-compartment model was still often selected, although now at a significantly reduced frequency. Second, in the case where the drug interaction covariate was simulated, the covariate was also introduced into V of the one-compartment model. Inclusion of the covariate on V finally brought the frequency of choosing the one-compartment model closer to that reasonably expected.

Results

Based on the results presented in Table I, data simulated with the covariate on CL and within the time range 12–120 hr were chosen to investigate covariate detection. Regardless of the covariance structure, the frequency of detecting the covariate effect, when it truly existed, was always higher using a two-compartment model than a one-compartment model (Tables II and III). When no covariance between CL and Vc (V) was included, the rate of detecting the covariate on CL was 87% for the two-compartment model and 72% for the one-compartment model. When a

Table II. Percentage of Two-Compartment Runs in which the Criterion for Detecting the Covariate was Satisfied[a]

Statistical model (Analysis)	% of runs selecting a covariate[b]				
	on *CL* only	on *Vc* only	on *Vc* in presence of covariate on *CL*	on *Vss* only	on *Vss* in presence of covariate on *CL*
No covariance between *CL* and *Vc*	87	15	4	2	4
Covariance between *CL* and *Vc*	83	52	8	2	5

[a]All results are based on a 1 degree of freedom chi-square test; a significance level of 0.001, corresponding to a difference in objective function values of 10.83, was used.
[b]50 data sets were simulated, in each of which 25 of the 100 subjects had a 25% higher *CL*.

covariance between *CL* and *Vc* (*V*) was included, the rate of detecting the covariate on *CL* was 83% for the two-compartment model and 58% for the one-compartment model.

The mean (±SE) estimates of *CL* in the two subpopulations (without and with the covariate effect) over the 50 data sets, using the two-compartment model, were 11.3±0.6 and 14.5±1.4 L/hr, respectively. (Recall, the true values are 11.3 and 14.2 L/hr, respectively.) These values with the one-compartment model were, however, overestimated, 15.8±1.0 and 19.5±1.4 L/hr.

Tables II and III also show the rate of falsely detecting the drug interaction covariate as acting on the volume parameters (*Vc* and *Vss* in the two-compartment model, and *V* in the one-compartment model). For the two-compartment model, there was a high incidence of false positive covariate effects on *Vc*, but only when the covariate effect on *CL* was omitted from the analysis. When the covariate effect was included on *CL*, there was a considerable difference between the estimates of *Vc*: 75.2±87.0 L (monotherapy group), and 44.0±56.0 L (drug interaction group). Consistent with the low rate of false positives, this difference was, however, imprecisely estimated as indicated by the large standard errors. The estimates of *Vss* for

Table III. Percentage of One-Compartment Runs in which the Criterion for Detecting the Covariate was Satisfied[a]

Statistical model (Analysis)	% of data sets detecting a covariate[b]		
	on *CL* only	on *V* only	on *V* in presence of covariate on *CL*
No covariance between *CL* and *V*	72	10	66
Covariance between *CL* and *V*	58	2	62

[a]All results are based on a one degree of freedom chi-square test; a significance level of 0.001, corresponding to a difference in objective function values of 10.83, was used.
[b]50 data sets were simulated, in each of which 25 of the 100 subjects had a 25% higher *CL*.

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8	2	5

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V only	on *V* in presence of covariate on *CL*
10	66
2	62

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5 of the 100 subjects had a 25% higher *CL*.

the two subpopulations were very similar, regardless of whether the covariate effect on *CL* was included in the analysis, and is reflected in the low rate of false positives.

With the one-compartment model, there was a high incidence of falsely detecting the covariate acting on *V*, especially when the covariate effect on *CL* was included in the analysis (Table III). Consistent with this finding, the estimates of *V* for the two subpopulations differed, and were precisely estimated: 816 ± 16 L (monotherapy group), and 923 ± 34 L (drug interaction group).

REAL DATA

To investigate whether the issues raised with the simulated data might be reflected in real data, two real data sets, which have been reported previously (25,6), were also analyzed.

Quinidine

Briefly, 391 serum quinidine concentrations from 139 adult hospitalized men, collected for routine clinical purposes, were available for analysis (25). The following demographic data were recorded: age, height, weight, race, smoking background, alcohol history, α-1-acid glycoprotein concentration ($\alpha_1 AGP$), presence/absence of congestive heart failure (CHF), presence/absence of dialysis or hemoperfusion, and high/low creatinine clearance (CrCL). Verme *et al.* found that the fit of the two-compartment model was no better than that of the one-compartment model (personal communication). We confirmed this finding by comparing the two models in the absence of covariate relationships, as well as in the presence of the covariates found by us to be statistically significant with the one-compartment model. These final covariates on *CL* included minor (difference in objective function values of the reduced and full models of 4–10) influences of race, height, weight, CrCL status and dialysis status, and major (objective function difference >10) influences of current drinking status and $\alpha_1 AGP$. A major influence of $\alpha_1 AGP$ was also found on *V*. Consistent with the original report, we found that a hyperbolic relationship between *CL* and $\alpha_1 AGP$, and between *V* and $\alpha_1 AGP$, could be supported.

The covariates found to be significant with the one-compartment model were then used with a two-compartment model and tested by stepwise deletion. Height and CrCL status, which were minor influences on *CL* in the one-compartment model, were negligible and major, respectively, using a two-compartment model. Most interesting, $\alpha_1 AGP$, identified as a major

influence on V in the one-compartment model, was found to have a negligible effect on Vc in the two-compartment model.

All models included covariances among ka, Vc (V), and CL. There was nothing remarkable about the estimates of these covariances, except that with both one- and two-compartment models, ka and Vc (V) were highly correlated.

Netilmicin

The netilmicin data used in our analysis was a combination of the primary and validation data sets collected from 102 neonates of 27 to 42 weeks gestational age (6). Netilmicin was given intravenously or intramuscularly in a dosage of 3 to 5 mg/kg once daily. Two to 12 netilmicin serum concentrations per neonate (344 total) were measured. Most neonates had measurements collected at target times of 2, 8, and 16 hr postdose. The following demographic data were recorded: gestational age, weight, length, age at the start of therapy, age on the day of concentration measurement, and creatinine clearance.

A two-compartment model could be justified statistically to describe the data (objective function value decreased 151, relative to that for the one-compartment model). As with the simulations, the aim of the present analysis was to compare covariate models when the choice of structural model is equivocal. Therefore, the data set was modified by removing all concentrations taken before 5 hr postdose, resulting in 217 concentrations from 101 neonates. The one-compartment model no longer differed statistically from the two-compartment model.

The major covariates affecting CL (objective function difference >30) using the one-compartment model, included weight, age on the day of concentration measurement, and gestational age. For V, a major influence of weight, and a minor (objective function difference 4–10) influence of gestational age were found. As described previously for quinidine, the same covariate model was then applied to a two-compartment model, and stepwise deletion of covariates was carried out. When a two-compartment model was used, the influences of both weight and gestational age on Vc were no longer found to be statistically significant.

All models used covariances between Vc (V) and CL. With both the one- and two-compartment models, CL and Vc (V) were highly correlated.

DISCUSSION

Selection of the "correct" model has usually been based upon (i) statistical criteria that assess the improvement in fit as the model increases in complexity, and (ii) a principle of parsimony. A simpler model is chosen

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over a more complex model only if statistically justifiable, i.e., if the fit obtained with each model is essentially the same. In this context, what is usually meant by simpler and more complex models is that the parameter space of the simpler model is embeddable in the parameter space of the more complex model. Often, one model for covariates can be regarded as simpler than another, given the *same* structural model. A one-compartment model is generally a simpler model than a two-compartment model.

Which overall model, including structural, covariate, and statistical submodels, is correct? Our results show that the correct covariate and statistical submodels can differ for two different structural submodels. Moreover, the least parsimonious covariate and statistical submodels can be associated with the most parsimonious structural submodel. Our calculations and simulations clearly illustrate and explain how choice of the simpler structural submodel can be justifiable statistically, but incorrect, insofar as with this choice, both the covariate and statistical submodels contain artifactual elements.

Our analyses of the quinidine and netilmicin data suggest that these considerations might also apply to real data. But they also suggest that the data analyst is faced with a fundamental uncertainty regarding which model is correct. With both analyses, the number of important covariates was fewer with the two-compartment model. In particular, with quinidine and the two-compartment model, the influence of $\alpha_1 AGP$ on *Vc* was negligible. Moreover, quinidine is known to follow two-compartment pharmacokinetics. Therefore, it is possible that when the data are analyzed with a one-compartment model, the apparent significant influence of $\alpha_1 AGP$ on *V* is artifactual, and the use of this model is incorrect.

Alternatively, with a highly protein-bound drug like quinidine, one might expect an influence of $\alpha_1 AGP$ on volume (33). Under the two-compartment model, one might expect an influence on *Vss*, if not on *Vc*. However, as with *Vc*, the influence of $\alpha_1 AGP$ on *Vss* appears not to be small, but it is not significant, which is to say that a considerable influence might exist, but the data do not support it. The uncertainty in the magnitude of the influence is considerable, and may arise simply because the two-compartment model is overparameterized. This situation is somewhat similar to the one with our simulations, where the influence of the interacting drug on either of the volume parameters for the two-compartment model truly did not exist. When we included the influence of the interacting drug covariate on the volume parameters of the two-compartment model, the influence on *Vc* was considerable, although not significant, while the influence on *Vss* was very small. In summary, it is also possible that the use of a one-compartment model is adequate and that for the most part, the influence of $\alpha_1 AGP$ on *V* is "real."

Interestingly, if there is a real effect of $\alpha_1 AGP$ on Vss, one would expect it to be characterized by a hyperbolic relationship, and with a drug like quinidine which has a large volume of distribution, also expect there to be no intercept term. This relationship is just the type we observed between $\alpha_1 AGP$ and Vss (two-compartment model) and also between $\alpha_1 AGP$ and V (one-compartment model), lending some credence to the correctness of the simpler, one-compartment model.

Nevertheless, we have demonstrated that, theoretically, there must be some degree of artifactual influence of $\alpha_1 AGP$ on V. So it is also possible that the influence of $\alpha_1 AGP$ on V is partly artifactual and partly real. If this combination of influences were true, it could help explain why the effect of $\alpha_1 AGP$ appeared to be stronger on V (one-compartment model) than it was on Vss (two-compartment model). We have not found a report in the literature that describes the magnitude of the effect of $\alpha_1 AGP$ on quinidine's Vss. The situation is similar with netilmicin, another drug known to follow two-compartment pharmacokinetics. The effect of weight on V may be artifactual, real, or a combination. There does not seem to be a way to resolve the uncertainty.

Consider the case in which a covariate was found to significantly influence more than one parameter (e.g., CL and V) of the one-compartment model, but, based on a priori information, its influence on one of these parameters (e.g., V) is entirely unreasonable. Then, when a two-compartment model was fit to these data, no unreasonable significant influence of a covariate on a parameter (e.g., Vc) was found to exist. One might comfortably conclude that the one-compartment model was incorrect, and its use led to an incorrectly identified covariate. Unfortunately, the ability to make such an unequivocal decision was not possible with either real data set we analyzed. We are only in a position to caution readers about the matter of model choice. Either a one-compartment model with associated covariates and covariances will be unquestionably incorrect, or there will be uncertainty about their correctness.

Based on our experience, the following scheme could be useful when building models during population analysis. First, a comparision of structural models without covariates should be made. The simplest supportable structural model should be used for building the covariate model, simply because the NONMEM program will run much faster during covariate selection. Second, possible influences of covariates on all pharmacokinetic parameters of the simpler structural model should be assessed, because, as we have emphasized, covariate effects (whether real or artifactual) can influence more than one parameter. Third, if a more complicated structural model seems to be a priori equally likely, then the covariate model built with the simpler structural model (including marginally significant covariates) should be used

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lysis. First, a comparision of struc-
be made. The simplest supportable
ilding the covariate model, simply
n much faster during covariate selec-
riates on all pharmacokinetic param-
uld be assessed, because, as we have
al or artifactual) can influence more
complicated structural model seems
variate model built with the simpler
significant covariates) should be used

with the more complicated structural model. Covariates rejected with the simpler model may then need to be reconsidered. Finally, covariates can be retested by stepwise deletion.

This paper has addressed model choice that was made ambiguous by censoring the data in the distribution phase. Whether or not the results can be extrapolated to models and data types other than the few studied here, they do indicate that careful consideration of the structural model must be made when building a population model. Optimally, the structural model should be defined prior to population analysis, based on experimental data (e.g., in Phase I or early Phase II). Further, as our investigation has demonstrated, ignoring likely candidates for the structural model, in the interest of simplicity, can be consequential in the selection of covariate and covariance models. Finally, if prior information about the structural model is weak or lacking, then inspection of the interaction between structural model, covariates, and covariances may hold important information about the appropriateness of different structural models.

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